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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/008,244	11/07/2001	Alan Huang	018781-005510US	6997

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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 04/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/008,244	HUANG ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-104* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-33* is/are allowed.

6)☒ Claim(s) *34-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicants are required under 35 U.S.C. §121 to elect a specie for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable

Applicant is advised that a response to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a generic claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are witten in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP 809.02(a).

Should applicant traverse on the ground that the species are not patentable distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. §103 of the other invention.

On 3/10/04, Joseph Snyder elected the species of example 6k, page 46.

✧

35 U.S.C §101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture or composition of matter or any new and useful improvement therof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 65-97 are rejected under 35 USC §101 because the claimed invention is not supported by a well established utility.

The cited claims are drawn to a method of "modulating" a STAT6-dependent condition. The term "modulating" would encompass an amelioration of the STAT6-dependent condition. Certainly, there is no question that diseased animals would benefit from an

amelioration of their adverse condition; this ground of rejection is not directed at such embodiments. But the term "modulating" would also encompass an exacerbation of the STAT6-dependent condition. It is to this embodiment that this ground of rejection is directed. For example, if an human subject is suffering from psoriasis or urticaria, what possible patentable utility would there be in worsening or exacerbating these conditions? Applicants are requested to explain how such a patient would benefit. If there is no benefit or purpose, then it would appear that patentable utility is lacking.

A secondary issue pertains to the situation where a patient is entirely healthy to begin with, and for whom administering a compound of claim 1 would provide no perceptible change (for better or worse) in his "condition". In other words, claim 65 encompasses the possibility of administering the compound to a subject who is not in need of the "modulating". If, as a hypothetical matter, there were no objection to the term "modulating" (which there is), this second ground of rejection could be overcome by reciting that the host is in need of the modulating. However, if the term "modulating" remains in the claim, the cited claims will remain rejected.

Claims 65-97 are also rejected under 35 USC §112 first paragraph. Specifically, since the claimed invention is not supported by a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

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The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33-104 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is stated (page 49, line 4+) that the compounds listed in table 3 were evaluated using a STAT6 DNA binding assay using BJAB cells, and that the listed compound exhibited an IC_{50} value below 100 mM. Also stated (page 42, line 17+) is that the compounds listed in table 1 exhibited an IC_{50} value below 50 micromolar, using the assay described in USP 6,207,391. Based on these in vitro assays, applicants are extrapolating to treatment of various diseases such as allergic rhinitis, asthma, atopic dermatitis, contact dermatitis, anaphylaxis, food or drug induced allergy, conjunctivitis, uveitis, hypersensitivity reactions, alveolitis, psodasis, Chtlrg-strauss syndrome, delayed - type hypersensitivity, urticaria, angiodema, eczema, scleroderma, and systemic lupus erythematosus. However, such an extrapolation lacks enablement.

As conveyed in Wurster A L (*Oncogene* **19** (21) 2577-84, 2000), STAT6 possesses the following domains: (a) a central DNA-binding domain, (b) a conserved SH2 domain for

dimerization, (c) an SH3 domain, (d) a C-terminal transactivation domain and (d) an amino terminal domain (130 amino acids) which promotes tetramerization of dimerized STAT6 molecules thereby enabling cooperative DNA binding on the promoters containing multiple potential STAT recognition sites. Thus, the selected site is critical. It remains unknown to which domain within the intact STAT6 protein the claimed peptides might bind and what the consequences of such binding might be following phosphorylation and dimerization. It is unkown whether tyrosine phosphorylation (on STAT6) will be inhibited, and if it is inhibited, what the manifestations of that inhibition might be in a patient afflicted with one of the allergic or hypersensitivity reactions listed in claim 97. Do the compounds bind to the SH2 region and inhibit both dimerization and translocation, or do the compounds inhibit binding between STAT6 and the IL-4 receptor? Even if it is true that one of these occurs, it does not necessarily follow therefrom that the disorders recited in claim 97 can be effectively treated even if binding between STAT6 and the IL-4 receptor can be inhibited.

The disclosure of Kuperman (*J Exp Med.* **187**, 939, 1998) is acknowledged; this reference shows that STAT6-deficient mice do not develop eosinophila or airway hyperresponsiveness following allergen sensitization and challenge. However, apart from the fact that STAT6-deficient mice represent a very different situation from mice which have been administered compounds which might bind to one particular region of STAT6, airway hyperresponsiveness following allergen sensitization is not representative of the various

conditions that are listed in the claims (e.g., claim 97). Type-I, II, III and IV hypersensitivity reactions are described briefly on page 301 of Roit (*Immunology*, 5th Edition, Mosby International, 1998); further discussion of Type-I hypersensitivity reactions can be found in chapter 23 of Roit, and further discussion of Type-IV hypersensitivity reactions can be found in chapter 26 of the same book. Asthma is a so-called Type-I hypersensitivity reaction and is different from the other hypersensitivity types, and different from the other recited conditions (dermatitis, rhinitis, asthma, scleroderma, eczema, conjunctivitis, cancer, transplant rejection, anaphylaxis, food allergies, hypersensitivity reactions, alveolitis, uricaria, angiodema and SLE). As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. With regard to the issue of "unpredictability", consider the following:

- Tomkinson A (*American Journal of Respiratory and Critical Care Medicine* **160** (4) 1283-91, 1999) reaffirms the result of Kuperman (*J Exp Med.* **187**, 939, 1998). which shows that STAT6-deficient mice do not develop eosinophila or airway hyperresponsiveness following allergen sensitization and challenge. However, the reference also discloses (e.g., p. 1290, col 1) that in the presence of IL-5, these same STAT6-deficient mice did develop eosinophila and airway hyperresponsiveness to allergen challenge. Thus, it may be the case that if one could block 100% of any and all functions of STAT6, some benefit would accrue to certain categories of

asthma sufferers who had been exposed to certain allergens. But even if this is true, the result with IL-5 demonstrates that STAT6 does not have a "monopoly" on inflammatory processes, and that there are many other agents which can act to cause inflammation, irrespective of STAT6. Moreover, Trifilieff, A (*British Journal of Pharmacology* **130** (7) 1581-8, 2000) discloses that abrogation of lung inflammation in STAT6-deficient mice is dependent on the allergen inhalation procedure. Thus, even if it were possible to block 100% of all STAT6 function (using the claimed compounds), questions would still exist about which categories of asthma suffers would benefit, in response to which allergens, and under what conditions of administration.

- Foster, P. S. (*Clinical and Experimental Allergy* **29** (1) 12-6, 1999) discloses (page 13, col 1) that anti-IL-4 mAb's are effective in attenuating airway hyperresponsiveness if administered during the primary sensitization phase, but not during the period or direct provocation of the airways with allergen. This raises the issue of the timing of administration of the potentially "active agent", and raises the possibility that, even if the claimed compounds are effective to inhibit bronchoconstriction if administered before allergen challenge, they might not be effective if administered after symptoms of bronchoconstriction had already developed. The claims encompass both possibilities.

- Henderson (*J. Immunol.* **164**, 1086-95, 2000) discloses that administration of soluble IL-4 receptor (sIL-4R) prior to OVA challenge inhibited the inflammatory response, but only if administered intranasally. If administered i.p., the sIL-4R was not effective. This raises the possibility that even if the claimed compounds are effective to inhibit bronchoconstriction if administered directly to the lung, they might not be effective if adminstered orally. The claims encompass both possibilities.

- Durbin J E (*Cell* **84** (3) 443-50, 1996) discloses that STAT1-deficient mice are immunodeficient, and susceptible to viral disease. The reference is silent as to whether STAT6-deficient mice are similarly affected. However, given the similarities in structure and function between STAT1 and STAT6, a significant possibility exists that STAT6-deficient mice would be similarly affected. Accordingly, if it is indeed true that the claimed compounds cause a significant and consequential reduction of STAT6 activity *in vivo*, the result could be the replacement of a mild allergic reaction with a serious viral infection.

- Wang, L. H. (*Blood* **95** (4) 1249-57, 2000) discloses that a "decoy" molecule was

able to block STAT6 binding to a cis-element probe and transactivation, but did not affect STAT6 phosphorylation, or expression of IL-4 receptor, or the interaction of STAT6 with the IL-4 receptor. The point of this is that it is possible to block one of the functions of STAT6 without blocking any other functions. In STAT6-deficient mice, all STAT6 functions are eliminated; even if applicants' assertions about the binding of the claimed compounds to STAT6 are true, it would not follow therefrom that all STAT6 functions would be blocked, and so extrapolation from results in STAT6-deficient mice leads to "unpredictable" results.

- Mikita (*J. Biol. Chem.* **273**, 17634, 1998) conducted mutational analysis of the STAT6 SH2 domain. The authors identified amino acids that are required for both DNA binding, and IL-4R interactions, as well as residues that, when mutated, impair only one of the two functions. This reference underscores the point that the two principle functions of STAT6 can be selectively inhibited, and one can expect different results in each case, unlike the results obtained with STAT6-deficient mice by Kuperman (*J Exp Med.* **187**, 939, 1998). In addition, this reference also supports the proposition that in selecting a specific region of STAT6 to inhibit binding, as applicants have apparently done, one cannot "predict" the outcome of such attempts at binding inhibition.

Thus, (a) the experimental basis on which all of applicants' extrapolations depend is highly suspect, and not fully defined. Using small peptides to mimick interactions of large, multifacted and multifunctional proteins is likely to lead to an unpredictable outcome if tested *in vivo*; (b) it remains unknown what degree of inhibition of binding between the STAT6 and IL-4R is possible *in vivo*, or even *in vitro*, and whether it is sufficient to be effective to treat any of the recited inflammatory conditions; (c) Even if it is possible to significantly reduce the interaction between STAT6 and IL-4R, the remaining functions of STAT6, including transactivation are not likely to be affected. The outcome of such selective inhibition, even if it is possible, is unknown; (d) even if it is possible to provide

some relief to certain categories of asthma suffers, questions remain about the allergens against which it will be effective, the conditions of administration, the timing of adminstration, and routes of administration; (e) even if it is possible to provide some relief to certain categories of asthma suffers, asthma is not representative of the various other conditions listed in claim 97.

In view of the foregoing, it is apparent that "undue experimentation" would be required by the skilled physiologist to practice the claimed invention.

Claims 33-64 are rejected because of the term "pharmaceutical". This term carries with it the implied assertion of therapeutic efficacy, which is not in evidence. It is suggested that the term "pharmaceutical" be deleted at every occurrence.

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The Japanese patents were stricken from the IDS. The record should be clear that only the abstracts were considered. It is suggested that applicants submit an IDS which makes this clear. The following can be listed in the "other documents" section of the IDS (and not the "foreign patent" section):

English Abstract of JP 10175964

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at 571-272-0951. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

DAVID LUKTON
PATENT EXAMINER
GROUP 1600